solution, from which part of the product crystallized spontaneously, was poured into an excess of ice–water; the *acid* (5·4 g., 50%) was recrystallized from 50% aqueous ethanol, m.p. 225° (decomp.) (Found: C, 38·5; H, 1·9; F, 9·0; S, 14·9. $C_7H_4NFO_4S$ requires C, 38·7; H, 1·9; F, 8·80; S, 14·8%); $\nu_{max.}$ (KBr) 1700, 1095, and 1020 cm.$^{-1}$.

2-Fluoro-3-(1-naphthyl)acrylic Acid.—The *ethyl ester* obtained in dibutyl ether from (I) and 1-naphthaldehyde in 48% yield had b.p. 145—148°/0·5 mm., $\nu_{max.}$ (KBr) 1730 and 1630 cm.$^{-1}$ (Found: C, 73·5; H, 5·4; F, 7·7. $C_{15}H_{13}FO_2$ requires C, 73·8; H, 5·3; F, 7·8%). Alkaline hydrolysis as described gave the *free acid* (90%), m.p. 160° (Found: C, 72·3; H, 4·4; F, 8·7. $C_{13}H_9FO_2$ requires C, 72·2; H, 4·2; F, 8·8%); $\nu_{max.}$ (KBr) 1700, 1630, and 1100 cm.$^{-1}$.

2-Fluoro-4,5-benzinden-1-one (VIII).—A mixture of the preceding acid (3 g.) and polyphosphoric acid (60 g.) was heated at 140° for 3 hr.; part of the product sublimed on to the colder parts of the reaction vessel. The solution was diluted with water and the *product* (1 g., 30%) filtered and sublimed at 150—160°/30 mm., m.p. 147°. The solution in ethanol showed a violet and that in concentrated sulphuric acid a yellow-green fluorescence (Found: F, 9·8. $C_{13}H_7FO$ requires F, 10·0%).

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Studies in the Indole Series. Part IV.[1] Tetrahydro-1*H*-pyrido[4,3-*b*]-indoles as Serotonin Antagonists

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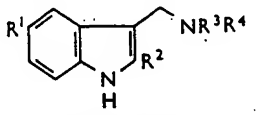
A series of tetrahydro-1*H*-pyrido[4,3-*b*]indoles has been made by Fischer cyclisation of arylhydrazones of 1-substituted-4-piperidones. Some of these compounds have been shown to have high anti-serotonin activity when submitted to pharmocological tests *in vitro*.

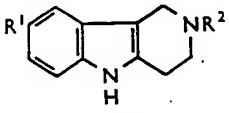
In the course of our studies of indole derivatives we investigated antagonists of 5-hydroxytryptamine (serotonin, 5-HT).

Compounds which prevent or block the pharmacological actions of serotonin are of considerable interest as tools for the study of the manifold functions of this hormone or neurotransmitter and of 5-HT-mediated drug actions. The synthesis of 5-HT antagonists was also encouraged by the possibility of more practical applications such as the management of conditions in which excessive action of 5-HT is known or postulated, *e.g.*, in migraine, 5-HT productive carcinoid, and certain types of asthma and allergy; 5-HT antagonists have also been considered as an approach to treatment of certain forms of hypertension. So far such antagonists have not established a clear position in therapy, although the potent antagonist 1-methyl-D-lysergic acid butanolamide (methysergide), has been introduced for the prophylaxis of migraine, and cyproheptadine, which combines anti-serotonin and anti-histaminic activities and is used in the treatment of allergic conditions such as urticaria.[2] Numerous indole derivatives, closely or distantly related to 5-hydroxytryptamine, have been found to be active as antagonists.[3]

Among the simpler types of compound are 5-benzyloxygramine[4] (I) and 5-chloro-2-methylgramine[5] (II).



(I) R^1 = $PhCH_2O$, R^2 = H, R^3 = R^4 = Me
(II) R^1 = Cl, R^2 = R^3 = R^4 = Me



(III) R^1 = R^2 = H
(IV) R^1 = Br, R^2 = Me.

In a search for new compounds with anti-serotonin activity, we examined modifications of (II) in which the basic side-chain at position 3- was linked cyclically to the 2-position in the form of a tetrahydro-γ-carboline derivative (2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole). Only a few compounds of this type have been described previously. The parent compound (III) was obtained by reduction of the corresponding pyrido[4,3-*b*]indole with sodium and n-butanol,[6] while substituted members of the series have usually been prepared by cyclisation of phenylhydrazones of 4-piperidones.[7] The 8-bromo-2-methyl derivative (IV) was first prepared by Boekelheide and Ainsworth[7a] as an intermediate for the N(2)-quaternary salts. A study of this compound and some halogen-free, 2-alkyl and 2-aralkyl derivatives for their action on the central nervous system has recently been published by Spickett.[8] Serotonin antagonism

[1] Part III, B. Heath-Brown and P. G. Philpott, *J. Chem. Soc.*, 1965, 7185.

[2] L. S. Goodman and A. Gilman, 'The Pharmacological Basis of Therapeutics,' Macmillan, New York, 1965, p. 651.

[3] (*a*) V. Erspammer, 'Drug Research,' ed. E. Jucker, Birkhäuser, Basle, 1961, 3, 270; (*b*) S. Garattini and L. Valzelli, 'Serotonin,' Elsevier, Amsterdam, 1965, p. 88.

[4] J. H. Gaddum, K. A. Hameed, D. E. Hathway, and F. F. Stephens, *Quart. J. Exp. Physiol.*, 1955, 49, 49.

[5] G. Quadbeck and E. Röhm, *Z. physiol. Chem.*, 1954, 297, 229; V. Colo, B. Asero, and A. Vercellone, *Farmaco (Pavia), Ed. Sci.*, 1954, 9, 611.

[6] R. Robinson and S. Thornley, *J. Chem. Soc.*, 1924, 2174.

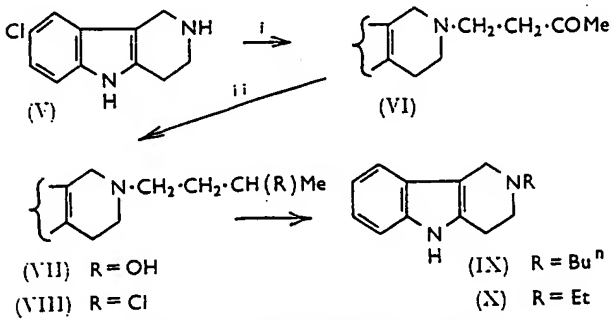
[7] (*a*) V. Boekelheide and C. Ainsworth, *J. Amer. Chem. Soc.*, 1950, 72, 2132. (*b*) A. H. Cook and K. J. Reed, *J. Chem. Soc.*, 1945, 402; W. Hörlein, *Chem. Ber.*, 1954, 87, 463; N. K. Kochetkov, N. F. Kucherova, L. P. Pronina, and M. I. Petruchenko, *Zhur. obschchei. Khim.*, 1959, 29, 3620 (*Chem. Abs.*, 1960, 54, 19665). (*c*) V. Rosnati and G. Palazzo, *Gazetta*, 1954, 84, 644; N. F. Kucherova and N. K. Kochetkov, *J. Gen Chem.* (*U.S.S.R.*), 1956, 26, 3511.

[8] R. G. W. Spickett, *J. Medicin. Chem.*, 1966, 9, 436.

in this series of compounds has not been reported previously.

In the present study, 2-alkyl and 2-aralkyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles were prepared by the Fischer cyclisation procedure with ethanolic hydrogen chloride, usually without isolation of the phenylhydrazones. In a few cases where this procedure failed, the hydrazones were isolated and cyclised with polyphosphoric acid or an acetic acid–sulphuric acid mixture.

The first group of compounds synthesised (Table 1) were directly related to the 5-chlorogramine structure and were prepared from *p*-chlorophenylhydrazine. Compounds (1)—(10) and (18) were obtained from the appropriate 4-piperidones; the remainder were obtained from the secondary base [(1), (V)] by further procedures.* Thus, reaction of this compound with methyl vinyl ketone yielded the ketone [(11), (VI)] which was reduced by sodium borohydride to the corresponding carbinol [(14), (VII)]. The latter was directly converted to the 3,4,5-trimethoxybenzoate (16) by means of the acid chloride and pyridine, and to the benzilate (17) by reaction with diphenylchloroacetyl chloride followed by mild hydrolysis. Proof of the



(V) (VI)

(VII) R = OH
(VIII) R = Cl
(IX) R = Bu^n
(X) R = Et

Reagents: i, CH_2:CH·COMe, ii, $NaBH_4$.

attachment of the oxobutyl group of the ketone (VI) to the N(2)-position rather than to the N(5)-position was obtained as follows: the carbinol (VII) was chlorinated and the product (VIII) was dehalogenated with excess of sodium in liquid ammonia. The resulting compound was 2-butyl-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indole [(22), (IX)] identical with that obtained from phenylhydrazine and 1-butyl-4-piperidone.

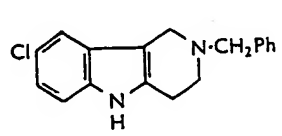
The 2-(β-hydroxyethyl) derivative (12) was obtained from the secondary base (V) and ethylene oxide. Its structure was similarly established by chlorination and reduction to the halogen-free compound (X), identical with the compound (21) synthesised from phenylhydrazine and 1-ethyl-4-piperidone. Reaction of the secondary base (V) with glycidol and ethyl acrylate gave compounds (13) and (15), respectively, the structures of which are assumed by analogy.

* For ease of identification, Arabic numbers are given to compounds appearing in Tables 1—3, and Roman numbers to structures appearing in the text.

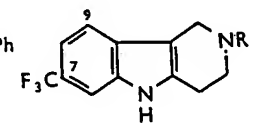
[9] E. J. Forbes, M. Stacey, J. C. Tatlow, and R. T. Wragg, *Tetrahedron*, 1960, 8, 67.

A number of 2-substituted 8-chloro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles showed high anti-serotonin activity, in particular the 2-methyl derivative [compound (2), Table 1; for a discussion of structure–activity relationships, see below]. This prompted examination of the corresponding known 8-bromo-compound (IV) and the synthesis of new analogues in which benzene ring substitution was studied. Table 2 shows those compounds (19)—(31) in which the benzene ring bears (a) either no substituent or one or two alkyl groups, (b) varying halogen substitution with and without additional alkyl groups, and (c) trifluoromethyl groups. Compound [(19), (III)] is known [6] and has now been prepared by hydrogenolysis of the 2-benzyl-8-chloro-derivative [(9), (XI)]. Similarly, hydrogenolysis of the 8-chloro-2-methyl analogue (2) yielded the known compound (20), previously obtained from phenylhydrazine and 1-methyl-4-piperidone.[7b]

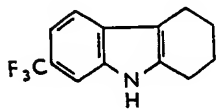
The structures of the compounds (21)—(28) and (31) are clear from their synthesis. Compounds (29) and (30) were obtained from 3-trifluoromethylphenylhydrazine and 4-piperidone and 1-methyl-4-piperidone, respectively, in each case as the sole product. The resulting structures could be formulated as (XII) by analogy with the similarly synthesised tetrahydrocarbazole (XIII).[9] Alternatively, the CF_3 group could be at the 9-position. According to Bornstein [10] cyclis-



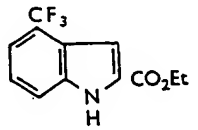
(XI)



(XII) R = H or Me



(XIII)



(XIV)

ation of ethyl pyruvate *m*-trifluoromethylphenylhydrazone yielded mainly the 4-trifluoromethylindole derivative (XIV). In the absence of rigorous proof of the structure (XII), compounds (29) and (30) have been designated as 7- or 9-trifluoromethyl derivatives. A compound probably identical with (30) was recently described by Aksanova *et al.*[11]

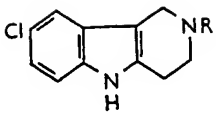
Table 3 summarises the data on tetrahydro-γ-carbolines substituted with hydroxy-, alkoxy-, or aralkoxy-groups in the benzene ring and hydrogen or lower alkyl groups at the 2-position.

Cyclisation of the *p*-benzyloxyphenylhydrazone of 1-methyl-4-piperidone proceeded unambiguously to give

[10] J. Bornstein, S. A. Leone, W. F. Sullivan, and O. F. Bennett, *J. Amer. Chem. Soc.*, 1957, 79, 1745.

[11] L. A. Aksanova, N. M. Sharkova, M. A. Baranova, N. F. Kucherova, and V. A. Zagorevskii, *Zhur. org. Khim.*, 1966, 2, 163 (*Index Chemicus* 65,005).

TABLE 1

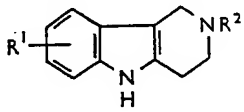


(R = Alkyl, aralkyl or substituted alkyl [a])

No.	R	M.p.	Yield (%)	Found (%) C	H	Cl	N	Formula	Required (%) C	H	Cl	N	Activity: Rat colon	Rat uterus
1	H	238—239°	50 [b]	64·1	5·5	17·0	13·3	$C_{11}H_{11}ClN_2$	63·9	5·4	17·1	13·5	3·0	6·5
2*	Me	195—196	58·5 [c]	65·7	6·0	16·1	12·6	$C_{12}H_{13}ClN_2$	65·3	5·9	16·1	12·7	100	100
3*	Me (with Ind–N–Me)	110—111·5	62·5 [c]	66·4	6·4			$C_{13}H_{15}ClN_2$	66·5	6·4			·3 /	6
4	Et	147—148	63 [c,d]	66·7	6·3	14·8	12·0	$C_{13}H_{15}ClN_2$	66·5	6·4	15·1	11·9	*ca.* 100	
5	Pr^n	129—130	61 [c,e]	68·1	7·0	14·1		$C_{14}H_{17}ClN_2$	67·6	6·9	14·2		*ca.* 100	
6	Pr^i	185—186	70 [f]	68·2	6·7	14·5	11·3	$C_{14}H_{17}ClN_2$	67·6	6·9	14·2	11·3	0·3	0·4
7	Bu^n	139—140	44 [g]			13·6	10·9	$C_{15}H_{19}ClN_2$			13·5	10·7	112	120
8	Am^n	134—135	60 [c,h]	69·6	7·4			$C_{16}H_{21}ClN_2$	69·4	7·6			*ca.* 100	
9	$PhCH_2$	118—119	49·5 [c,i]	72·8	5·85		9·7	$C_{18}H_{17}ClN_2$	72·8	5·8		9·4		
10	$[CH_2]_2NEt_2$		56 [j,k]				13·35	$C_{17}H_{24}ClN_3$				13·7	5	4
11*	$[CH_2]_2COMe$	117	74·5 [c]	65·1	6·3	12·7	10·0	$C_{15}H_{17}ClN_2O$	65·1	6·2	12·8	10·1	45	40
12*	$[CH_2]_2OH$	*ca.* 66	58	61·9	6·1		11·0	$C_{13}H_{15}ClN_2O$	62·3	6·0		11·2	3	
13*	$CH_2CH(OH)CH_2OH$	*ca.* 80	39	59·1	6·1			$C_{14}H_{17}ClN_2O_2$	59·9	6·1			5	
14*	$[CH_2]_2CH(OH)Me$	169—170	84	64·6	6·85			$C_{15}H_{19}ClN_2O$	64·6	6·9			*ca.* 10	2·5
15*	$[CH_2]_2CO_2Et$	120	56	62·7	6·3	11·6		$C_{16}H_{19}ClN_2O_2$	62·6	6·2	11·55		40	
16*	3-(3,4,5-Trimethoxybenzoyloxy)butyl	177—178	31 [c]	63·7	6·1	7·7	6·0	$C_{25}H_{29}ClN_2O_5$	63·5	6·2	7·5	5·9	13	
17*	3-(Hydroxydiphenylacetoxy)butyl	136—138	47 [l]	66·0	5·8	13·6		$C_{29}H_{30}Cl_2N_2O_3$	66·25	5·75	13·5		15	
18	2-(3,4-Dimethoxyphenethyl)-	184—185	59 [c,m,n]	68·35	6·3		7·4	$C_{21}H_{23}ClN_2O_2$	68·0	6·25		7·6	>100	100

[a] *General Note to the Tables.* Compounds marked * were made by specific methods given in the Experimental section. The remaining compounds were made from the appropriate hydrazines and piperidones according to the general method given at the beginning of that section. Unless otherwise stated, the hydrazines and the piperidones were made by standard literature methods with slight variations in individual cases. Compounds were crystallised from ethanol unless otherwise stated. [b] *Maleate*, m.p. 194—195° (Found: C, 55·7; H, 4·7. $C_{15}H_{15}ClN_2O_4$ requires C, 55·8; H, 4·7%). The 2-*acetyl derivative* had m.p. 225° (Found: C, 62·85; H, 5·5; Cl, 14·2; N, 11·1. $C_{13}H_{13}ClN_2O$ requires C, 62·8; H, 5·3; Cl, 14·3; N, 11·3%). [c] Cryst. from benzene. [d] *Hydrochloride*, m.p. 259—261° from EtOH (Found: C, 57·8; H, 5·85; Cl, 26·1. $C_{13}H_{15}ClN_2$,HCl requires C, 57·6; H, 5·95; Cl, 26·1%). [e] *Maleate*, m.p. 152° (Found: C, 59·5; H, 5·8; N, 7·6. $C_{18}H_{21}ClN_2O_4$ requires C, 59·3; H, 5·8; N, 7·7%). [f] *Hydrochloride*, m.p. 262—263° from EtOH–H_2O (Found: Cl, 24·7; N, 9·8. $C_{14}H_{17}ClN_2$,HCl requires Cl, 24·9; N, 9·8%). *Maleate*, m.p. 187° (Found: C, 59·2; H, 5·7. $C_{18}H_{21}ClN_2O_4$ requires C, 59·3; H, 5·8%). [g] *Maleate*, m. p. 161° (Found: C, 60·1; H, 6·2. $C_{19}H_{23}ClN_2O_4$ requires C, 60·2; H, 6·1%). [h] *Maleate*, m.p. 163—164° (Found: C, 61·2; H, 6·5. $C_{20}H_{25}ClN_2O_4$ requires C, 61·1; H, 6·4%). [i] *Maleate*, m.p. 206—207° (Found: C, 63·7; H, 5·1. $C_{22}H_{21}ClN_2O_4$ requires C, 64·0; H, 5·1%). [j] B.p. 160°/10^{-3} mm. [k] *Dihydrochloride*, m.p. 228—229° from EtOH–Et_2O (Found: Cl, 27·5; N, 10·8. $C_{17}H_{24}ClN_3$,2HCl requires Cl, 28·1; N, 11·1%). [l] The m.p. yield and analysis are for the *hydrochloride of the base*, crystallised from n-butanol. [m] Prepared by the general method except that the *p*-chlorophenylhydrazine hydrochloride was neutralised with potassium acetate during the hydrazone formation. The base was sparingly soluble in benzene. It could also be crystallised from aqueous dioxan. [n] The *methanesulphonate*, m.p. 192—193°, crystallised from water (Found: C, 56·3; H, 5·8. $C_{22}H_{27}ClN_2O_3S$ requires C, 56·6; H, 5·8%).

TABLE 2



(R^1 = H, alkyl, halogen, or CF_3; R^2 = H or alkyl)

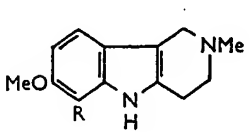
No.	R^1	R^2	M.p.	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N	Activity: Rat colon	Rat uterus
19*	H	H	215°	*a*				$C_{11}H_{12}N_2$				*ca.* 2·5	
20*	H	Me	171—172	*b, c*				$C_{12}H_{14}N_2$				*ca.* 10	*ca.* 20
21	H	Et	125	52 [d]	77·6	8·3	13·85	$C_{13}H_{16}N_2$	77·95	8·1	14·0		
22	H	Bu^n	111	51 [e]	78·9	8·8	12·2	$C_{15}H_{20}N_2$	78·9	8·8	12·3		
23	8-Me	Me	155	77 [f,g]			13·8	$C_{13}H_{16}N_2$			14·0	7·0	4
24	6,8-di-Me	Me	126	44 [c,h]			12·45	$C_{14}H_{18}N_2$			13·1	*ca.* 100	
25	8-Br	Me	188	60 [i]				$C_{12}H_{13}BrN_2$				110	
26	8-Cl-6-Me	Me	155—157	51 [c,j]	66·4	6·4	11·85	$C_{13}H_{15}ClN_2$	66·5	6·4	11·9	*ca.* 100	100
27*	6,7-di-Cl	Me	165	24	56·1	4·7		$C_{12}H_{12}Cl_2N_2$	56·5	4·7		100	100
28	6,8-di-Cl	Me	160	17 [c,k]			10·6	$C_{12}H_{12}Cl_2N_2$			11·0	100	100
29*	7(or 9)-CF_3	H	233	10 [l]	60·4	5·3	11·7	$C_{12}H_{11}F_3N_2$	60·0	4·6	11·7		
30*	7(or 9)-CF_3	Me	229—232	47 [m]	61·1	5·2	10·7	$C_{13}H_{13}F_3N_2$	61·4	5·15	11·0	*ca.* 100	
31*	8-CF_3	Me	180—182	59 [c]	61·3	5·3	10·9	$C_{13}H_{13}F_3N_2$	61·4	5·15	11·0	>100	>100

[a] Lit.,[6] m.p. 215·5°. Lit.,[8] m.p. 205—207°. [b] Lit.,[7b] m.p. 171—173°. [c] Cryst. from benzene. [d] Lit.,[8] m.p. 125—126°. [e] Cryst. from ethanol–light petroleum. [f] Cryst. from EtOAc. [g] *Hydrochloride*, m.p. 230° (Found: Cl, 15·3; N, 11·9. $C_{13}H_{16}N_2$,HCl requires Cl, 15·0; N, 11·8%). [h] *Hydrochloride*, m. p. 262—263° from N-HCl (Found: Cl, 14·0; N, 11·3. $C_{14}H_{18}N_2$, HCl requires Cl, 14·1. N, 11·2%). [i] Lit.,[7a] m.p. 185—186°. Lit.,[8] m.p. 165·5—167°. The *hydrochloride*, m.p. 268—269° crystallised from H_2O (Found: C, 58·0; Cl, 11·8. $C_{12}H_{13}BrN_2$, HCl requires Cl, 11·8%). Lit.,[8] m.p. 264°. [j] *Hydrochloride*, m.p. 265—267° from H_2O (Found: C, 58·0; H, 6·15. $C_{13}H_{15}ClN_2$,HCl requires C, 57·6; H, 5·95%). [k] Found: Cl, 27·2. $C_{12}H_{12}Cl_2N_2$ requires Cl, 27·8%. *Methanesulphonate* from EtOH–Et_2O, m.p. 226—227° (Found: C, 43·7; H, 4·65. $C_{13}H_{16}Cl_2N_2O_3S$ requires C, 44·4; H, 4·6%). [l] Cryst. from MeOH. [m] Cryst. from dioxan. A compound possibly identical with this has recently been described by Aksenova *et al.*[11]

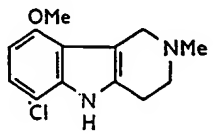
the expected 8-benzyloxytetrahydro-γ-carboline (41). Cyclisation of *m*-alkoxyphenylhydrazones could theoretically yield either 7- or 9-substituted derivatives. In our experiments only one compound was obtained in each case, exemplified by compounds (33), (39), and (40). These have been shown to have 7-substitution.

Orientation was established by the method used for tetrahydrocarbazoles by Cummins and Tomlinson,[12] and more recently by Campaigne and Lake and by Suvorov *et al.*[13] Accordingly, the 2-chloro-3-methoxyphenylhydrazone of 1-methyl-4-piperidone was cyclised unambiguously to the tetrahydrocarboline [(37), (XV)] with ethanolic hydrogen chloride. Treatment with sodium and liquid ammonia yielded a halogen-free compound (XVI) identical with compound (33) from *m*-methoxyphenylhydrazine and 1-methyl-4-piperidone. Demethylation of this 7-methoxy-compound yielded a phenol (44) identical with that obtained by dealkylation of the propoxy- and butoxy-derivatives (39) and (40). The orientation in compounds (32) and (34)—(36), prepared from *m*-methoxyphenylhydrazine and other *N*-alkyl 4-piperidones, is assumed by analogy. The ethyl ether (38) has undoubted 7-substitution since it has been prepared from the 7-hydroxy-compound by direct alkylation.

No 9-alkoxy-substituted isomers were found in the cyclisation products from *m*-alkoxyphenylhydrazones. To obtain such compounds the 2-chloro-5-methoxyphenylhydrazone of 1-methyl-4-piperidone was cyclised and the tetrahydrocarboline [(43), (XVII)] was dehalogenated by hydrogenolysis to 9-methoxy-2-methyltetrahydro-1*H*-pyrido[4,3-*b*]indole (42) which was different from the 7-methoxy-compound already discussed. Demethylation yielded the corresponding phenol (46).

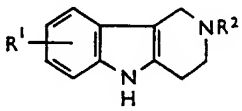


(XV) R = Cl
(XVI) R = H



(XVII)

TABLE 3



(R¹ = Alkoxy, hydroxy, or aralkoxy; R² = H or alkyl)

No.	R¹	R²	M.p.	Yield (%)	Found (%) C	H	Cl	N	Formula	Required (%) C	H	Cl	N	Activity: Rat colon	Rat uterus
32	7-MeO	H	214—215°	21 [a,b]	70·9	7·15		14·0	$C_{12}H_{14}N_2O$	71·3	7·0		13·9		
33*	7-MeO	Me	195—196	68	72·4	7·4		12·95	$C_{13}H_{16}N_2O$	72·2	7·45		12·95	*ca.* 2·5	
34	7-MeO	Pr^n	149—151	56·5 [c,d]	73·2	8·0		11·6	$C_{15}H_{20}N_2O$	73·7	8·25		11·5		
35	7-MeO	Pr^i	113—115	48 [c,e]	73·9	8·0		11·1	$C_{15}H_{20}N_2O$	73·7	8·25		11·5		
36	7-MeO	Bu^n	155—156	54 [f]	74·8	8·6		10·8	$C_{16}H_{22}N_2O$	74·4	8·6		10·8		
37	6-Cl-7-MeO	Me	194—195	41 [c,g]	62·6	6·0	14·2	11·1	$C_{13}H_{15}ClN_2O$	62·3	6·0	14·15	11·2	*ca.* 10	
38*	7-EtO	Me	199—200	20 [a]	73·0	7·9		12·1	$C_{14}H_{18}N_2O$	73·0	7·9		12·2	*ca.* 10	
39	7-Pr^{n}O	Me	159—160	35·5 [h]	74·0	8·3		11·5	$C_{15}H_{20}N_2O$	73·7	8·25		11·5	*ca.* 2·5	
40	7-Bu^{n}O	Me	164—165	66·5 [i]	74·4	8·6		10·9	$C_{16}H_{22}N_2O$	74·4	8·6		10·85	*ca.* 10	
41*	8-PhCH$_2$O	Me	234—235	58 [j]			10·7	8·5	$C_{19}H_{21}ClN_2O$			10·8	8·5	0·1	1·4
42*	9-MeO	Me	184—185	74 [a]	71·7	7·4		12·4	$C_{13}H_{16}N_2O$	72·2	7·45		12·95	*ca.* 10	
43	6-Cl-9-MeO	Me	189	25 [a,k,l]	59·1	6·0	13·2	10·2	$C_{14}H_{15}ClN_2O_2$	59·5	6·8	12·5	9·9	*ca.* 100	
44*	7-OH	Me	234—235	31 [a,m]	50·5	5·5		9·9	$C_{12}H_{15}BrN_2O$	50·9	5·35		9·9	<2·5	
45*	8-OH	Me	*ca.* 285	69 [j]	60·1	6·4	15·0	11·8	$C_{12}H_{15}ClN_2O$	60·4	6·3	14·9	11·7	0	1·6
46*	9-OH	Me	*ca.* 285	21 [n]				8·6	$C_{12}H_{17}BrN_2O_2$				9·3		

[a] Cryst. from MeOH. [b] *Hydrochloride*, m.p. *ca.* 255° (decomp.), from MeOH (Found: C, 59·65; H, 6·3. $C_{12}H_{14}N_2O$,HCl requires C, 60·4; H, 6·3%). [c] Cryst. from benzene. [d] *Hydrochloride*, m.p. 241—242° (Found: C, 63·75; H, 7·35; Cl, 12·3; N, 9·9. $C_{15}H_{20}N_2O$,HCl requires C, 64·1; H, 7·5; Cl, 12·6; N, 10·0%). [e] *Hydrochloride*, m.p. 240—241° (Found: C, 63·9; H, 7·6; Cl, 12·75; N, 10·0. $C_{15}H_{20}N_2O$,HCl requires C, 64·1; H, 7·5; Cl, 12·6; N, 10·0%). [f] *Hydrochloride*, m.p. 238—240° (Found: C, 65·1; H, 7·9; Cl, 11·8; N, 9·6. $C_{16}H_{22}N_2O$,HCl requires C, 65·2; H, 7·9; Cl, 12·0; N, 9·5%). [g] *Hydrochloride*, m.p. 271°, from MeOH (Found: C, 54·1; H, 5·4; Cl, 24·6; N, 9·6. $C_{13}H_{15}ClN_2O$,HCl requires C, 54·4; H, 5·6; Cl, 24·7; N, 9·8%). [h] *Hydrochloride*, m.p. 239—240° from N-HCl (Found: C, 64·6; H, 7·8; Cl, 12·8. $C_{15}H_{20}N_2O$,HCl requires C, 64·1; H, 7·5; Cl, 12·6%). [i] *Hydrochloride*, m.p. 236—237° from N-HCl (Found: C, 65·1; H, 8·0; Cl, 12·3. $C_{16}H_{22}N_2O$,HCl requires C, 65·2; H, 7·9; Cl, 12·0%). [j] Yield, m.p. and analysis are for the *hydrochloride* which cryst. from H_2O. [k] Analysis includes 1 mol. MeOH of cryst. [l] *Hydrochloride*, m.p. 282°, from N-HCl (Found: C, 51·2; H, 5·9; Cl, 23·5; N, 9·1. $C_{13}H_{15}ClN_2O$,HCl,H_2O requires C, 51·1; H, 5·9 Cl, 23·2; N, 9·2%). [m] Yield, m.p., and analysis are for the *hydrobromide*. [n] Yield, m.p., and analysis are for the *hydrobromide monohydrate* (Found: Br, 27·0. $C_{12}H_{14}N_2O$,HBr,H_2O requires Br, 26·5%).

Pharmacology.—The anti-serotonin activities of the compounds described here (Tables 1—3) have been determined *in vitro* on the isolated rat uterus and/or colon,[14] and we are grateful to Dr. M. W. Parkes for these results.

8-Chloro-2-methyl-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indole (2), an early active member of our series was assigned an arbitrary activity value of 100 in each test. On this scale some previously known serotonin

[12] J. A. Cummins and M. L. Tomlinson, *J. Chem. Soc.*, 1955, 3475.

[13] E. Campaigne and R. D. Lake, *J. Org. Chem.*, 1959, **24**, 278; N. N. Suvorov, M. V. Fedotova, L. M. Orlova, and O. B. Ogareva, *Zhur. obshchei Khim.*, 1962, **32**, 2358 (*Chem. Abs.*, 1963, **58**, 9007).

[14] J. H. Gaddum and K. A. Hameed, *Brit. J. Pharmacol.*, 1954, **9**, 240; J. H. Gaddum, W. S. Peart, and M. Vogt, *J. Physiol.*, 1949, **108**, 467.

antagonists are evaluated as follows: 5-benzyloxygramine = 200, lysergic acid diethylamide = 200, and methysergide = 500.

From Table 1 it can be seen that high anti-serotonin activity is attained with tetrahydro-γ-carbolines which have an 8-chloro-substituent together with a straight chain alkyl group in the 2-position [compounds (2), (4), (5), (7), and (8)]. High activity is also observed with the 3,4-dimethoxyphenethyl side chain [compound (18)]. Activity is reduced by the introduction of branched side-chains [compound (6)], or functional groups into the side-chain [compounds (10)—(17)] at position 2.

Substitution in the aromatic ring affects the activity as shown in Table 2. Provided the 2-methyl group is retained, the activity remains high when the 8-chloro-group is exchanged for another halogen [compound (25)], or for trifluoromethyl [compound (31), one of the most active of the series], or when the ring is substituted by more than one halogen group, by the 7-trifluoromethyl group, or even by two methyl groups [compounds (27), (28), (30), and (24)]. Oxygen substitution in the aromatic ring lowers activity substantially (Table 3) except for compound (43) where chlorine is also present.

It is of further interest to note that methylation of the N(5) position of compound (2) results in very considerably reduced activity [compound (3)]. By contrast, methylation of the indole-ring nitrogen of various lysergic acid amides causes a marked increase of anti-serotonin activity in the rat uterus preparation.[3a]

Summarising the tetrahydro-γ-carboline series as a whole, appropriately halogen-substituted *N*-alkyl derivatives show high *in vitro* activity of a similar order to, but probably slightly lower than, that of the open-chain analogue 5-chloro-2-methylgramine.

The effects of compound (2) on platelet aggregation have been reported;[15] further study of its pharmacological activity will be published by Dr. M. W. Parkes.

EXPERIMENTAL

Ether solutions were dried with activated calcium sulphate (Hydrite). Light petroleum had b.p. 60—80°. The figures in parentheses after the names of compounds correspond to those in column 1 of Tables 1—3.

All products were colourless, and salts were crystallised from ethanol or ethanol–ether unless otherwise stated. The u.v. spectra were determined with a Unicam SP 500 or Perkin-Elmer 137 spectrophotometer. The i.r. spectra were determined for chloroform solutions with a Unicam SP 200 spectrophotometer, and the n.m.r. spectra were recorded in deuteriochloroform using a Varian A.60 instrument.

General Method for the Preparation of Tetrahydro-γ-carbolines.—This is exemplified by the following details for 8-chloro-2,3,4,5-tetrahydro-2-methyl-1*H*-pyrido[4,3-*b*]-indole (2). *p*-Chlorophenylhydrazine hydrochloride (89·5 g., 0·5 mole), and 1-methyl-4-piperidone (56·6 g., 0·5 mole), were heated under reflux in ethanol (400 ml.) for 1 hr., and then diluted with ethanol (400 ml.); the mixture was then stirred under reflux and treated with dry hydrogen chloride for 1—1½ hr. The thick yellow suspension was cooled to 0°, the solid was collected, and the filtrate was evaporated under reduced pressure to a small volume. The residue, combined with the solid, was dissolved in hot water (800 ml.), treated with charcoal and filtered, and the clear solution was made alkaline with an excess of 2N-sodium hydroxide. The precipitated solid was cooled, filtered off, washed well with water, and dried. The crude material (86 g., m.p. 185—195°) was crystallised from benzene or ethanol and yielded the pure base (65 g., 58·5%), m.p. 195—196°, $\nu_{max.}$ 3460 cm.$^{-1}$ (NH), $\lambda_{max.}$ (EtOH) 231, 290, and 299, $\lambda_{min.}$ 256 and 297 (log ε 4·51, 3·79, 3·72, 3·18, and 3·69); τ 2·63 (1H, multiplet, ArH), 2·91 (2H, multiplet, ArH), 6·39 (2H, broadened singlet, $-CH_2-$), 7·21 (4H, singlet, $-CH_2\cdot CH_2-$), and 7·45 (3H, singlet, =NMe). The *hydrochloride* crystallised from water containing a little hydrochloric acid, m.p. 265—268° (Found: Cl, 27·7; N, 10·8. $C_{12}H_{13}ClN_2,HCl$ requires Cl, 27·6; N, 10·9%), $\lambda_{max.}$ (0·01N-hydrochloric acid) 279, 286, and 296·5, $\lambda_{min.}$ 248, 283, and 294·5 mμ (log ε 3·79, 3·78, 3·66, 3·33, 3·77, and 3·64). The *maleate* crystallised from water, m.p. 209—210° (Found: C, 56·8; H, 5·0. $C_{16}H_{17}ClN_2O_4$ requires C, 57·1; H, 5·1%). The *acetate* crystallised from glacial acetic acid–ether with 1 mole of acetic acid of crystallisation. M.p. after rapid heating, *ca.* 95° (decomp.), on slow heating all the acetic acid was lost and the m.p. of the base was obtained [Found (dried at 48° *in vacuo*): C, 56·4; H, 6·1. $C_{16}H_{21}ClN_2O_4$ requires C, 56·4; H, 6·2%]. The *methiodide* crystallised from water, m.p. 245—246° (Found: C, 43·1; H, 4·4.% $C_{13}H_{16}ClIN_2$ requires C, 43·0; H, 4·4%).

Most of the simpler compounds described in the Tables were made by the above method using the appropriate hydrazines and piperidones. In some cases ether extraction was used to recover the bases after the reaction mixture had been made alkaline. The bases were usually crystalline solids but, in a few cases viscous liquids were obtained after distillation.

8-*Chloro*-2,3,4,5-*tetrahydro*-2,5-*dimethyl*-1H-*pyrido*[4,3-b]-*indole* (3).— 8-Chloro-2,3,4,5-tetrahydro-2-methyl-1*H*-pyrido[4,3-*b*]indole (2) (6·62 g., 0·03 mole) was added in portions to a stirred suspension of sodamide in liquid ammonia [from sodium (0·69 g., 0·03 mole) and ammonia (100—150 ml.)]. After 1 hr. methyl iodide (1·87 ml., 0·03 mole) in dry ether (10 ml.) was added and the mixture was stirred for 3 hr. and then evaporated. The residue was treated with ice–water and the resulting solid was dried and extracted with hot alcohol to leave a residue (1·2 g.) of the methiodide of the starting material (see above). The alcohol extract yielded a product (4·4 g., 62·5%), which was recrystallised from benzene or light petroleum to give the *base* as white prisms, m.p. 110—111·5°. The i.r. spectrum showed no NH-band; $\lambda_{max.}$ (EtOH) 207, 236, and 294, $\lambda_{min.}$ 212, 255infl, 290, and 300 mμ (log ε 4·16, 4·53, 3·78, 4·15, 3·13, 3·75, and 3·73); τ 2·67 (1H, multiplet, ArH), 2·93 (2H, multiplet, ArH), 6·43 and 6·49 (total 5H, 2 singlets overlapping, $-CH_2-$ and NMe), 7·21 (4H, singlet, $-CH_2\cdot CH_2-$), and 7·49 (3H, singlet, NMe). The *methanesulphonate* had m.p. 225—226° (Found: C, 50·3; H, 5·7. $C_{14}H_{19}ClN_2O_3S$ requires C, 50·8; H, 5·8%).

1-(2-*Diethylaminoethyl*)-4-*piperidone*.—A mixture of 2-diethylaminoethylamine (34·2 g., 1 mol.) and ethyl acrylate

[15] J. R. O'Brien, *J. Clin. Pathol.*, 1962, **15**, 446; H. R. Baumgartner, A. Studer, and K. Reber, *Thromb. Diath. Haemorrh.* (Stuttg.), 1963, **9**, 485; A. J. Honour and J. R. A. Mitchell, *Nature*, 1963, **197**, 1019.

(70·2 ml., 2·2 mol.) was kept for 5 days and distilled, to yield a product, b.p. *ca.* 140—150°/0·2 mm.; the fore-run was given a second treatment with ethyl acrylate and then redistilled. The resulting *ethyl 2-diethylaminoethylimino-ββ′-dipropionate* (61·5 g., 66%) had b.p. 144—146°/0·2 mm. It was moderately soluble in cold, but less soluble in hot, water (Found: N, 8·8. $C_{16}H_{32}N_2O_4$ requires N, 8·9%).

Sodium ethoxide [from sodium (0·72 g., 0·0312 mole)] was suspended in dry toluene (15 ml.), and the above basic ester (9·87 g., 0·0312 mole), in toluene (10 ml.), was added. The mixture was then stirred and heated, while an ethanol–toluene azeotrope was removed through a short fractionating column. When all the ethanol had been removed, the mixture was heated for a further ½ hr. under reflux, cooled, and extracted three times with hydrochloric acid [(*a*) 8 ml. concentrated acid and 24 ml. water, (*b*) twice with 2 ml. concentrated acid and 6 ml. water]. The acid extract was heated under reflux for 6 hr., when it no longer gave a positive reaction with ferric chloride. It was evaporated under reduced pressure, treated with an excess of saturated potassium carbonate solution, and finally extracted continuously with ether for 8 hr. The dried extract yielded the *piperidone* (3·0 g., 49%), b.p. 99—100°/0·1 mm., n_D^{20} 1·4726 (Found: N, 14·3. $C_{11}H_{22}N_2O$ requires N, 14·1%).

8-*Chloro*-2,3,4,5-*tetrahydro*-2-(3-*oxobutyl*)-1H-*pyrido*-[4,3-b]*indole* (11).—8-Chloro-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indole (1), prepared by the general method (49·8 g., 1 mol.) was stirred in benzene (350 ml.), and treated with methyl vinyl ketone (18·6 g., 1·1 mol.) in benzene (20 ml.). The mixture was kept at 70° for 1 hr. and then at 10—15° for 20 hr. A solid (55 g.), m.p. *ca.* 110°, was filtered off, and the filtrate was evaporated under reduced pressure to give a gum. The solid was dissolved in benzene (2 l.) and then filtered through a column of alumina (Grade II, neutral) to yield pure material, m.p. 116—117° on evaporation. Similar treatment of the gummy residue yielded further crops. The *ketone* (49·8 g., 74·3%) crystallised from benzene, m.p. 117°. The *maleate* had m.p. 152° (Found: C, 58·1; H, 5·5. $C_{19}H_{21}ClN_2O_5$ requires C, 58·1; H, 5·4%).

8-*Chloro*-2,3,4,5-*tetrahydro*-2-(2-*hydroxyethyl*)-1H-*pyrido*-[4,3-b]*indole* (12).—8-Chloro-2,3,4,5-tetrahydro-1*H*-pyrido-[4,3-*b*]indole (1) (6·2 g., 1 mol.), and ethylene oxide (1·45 g., 1·1 mol.) in ethanol (20 ml.), were heated at 100° for 3½ hr. in a pressure bottle with occasional shaking. The solution was then evaporated under reduced pressure and the residue (7·2 g.) was distilled, b.p. 210°/0·03 mm. The *basic alcohol* (4·2 g., 58%) crystallised, m.p. *ca.* 66°. The *maleate* had m.p. 175° (Found: C, 55·7; H, 5·3. $C_{17}H_{19}ClN_2O_5$ requires C, 55·7; H, 5·2%).

2-*Ethyl*-2,3,4,5-*tetrahydro*-1H-*pyrido*[4,3-b]*indole* (21).—The above basic alcohol (2·8 g., 0·011 mole) in benzene (60 ml.) was treated with thionyl chloride (6·4 ml., 0·09 mole) and the mixture was heated under reflux for 4 hr. The solvent was evaporated, the residue was treated with an excess of dilute ammonia solution, and the product was extracted with benzene. Evaporation of the benzene gave a crude chloro-compound (1·7 g.) which was dissolved in tetrahydrofuran (50 ml.)–liquid ammonia (200 ml.) and reduced with sodium (0·6 g., 4 equivalents). After decomposition with ammonium chloride the mixture was evaporated and treated with benzene and water. The benzene layer yielded a crude halogen-free gum which was purified by column chromatography, and sublimation at 160°/10^{-3} mm. The sublimate was crystallised from ethanol to yield a product, m.p. 124°, which proved to be identical with compound (21), made from phenylhydrazine and *N*-ethyl-4-piperidone (Table 2).

8-*Chloro*-2,3,4,5-*tetrahydro*-2-(2,3-*dihydroxypropyl*)-1H-*pyrido*[4,3-b]*indole* (13).— 8-Chloro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (1) (2·24 g., 1 mol.), and glycidol (0·88 g., 1·1 mol.) were heated under reflux for 3 hr. in ethanol (20 ml.). Evaporation under reduced pressure yielded a product (3·2 g.) which was distilled, b.p. *ca.* 200° (bath temperature)/0·8 mm. The *glycol* (1·2 g., 39%) solidified to a yellowish solid, m.p. *ca.* 80°. The *maleate* had m.p. 190° (Found: C, 54·7; H, 5·4; N, 9·1. $C_{18}H_{21}ClN_2O_6$ requires C, 54·5; H, 5·3; N, 8·9%).

8-*Chloro*-2,3,4,5-*tetrahydro*-2-(3-*hydroxybutyl*)-1H-*pyrido*-[4,3-b]*indole* (14).— 8-Chloro-2,3,4,5-tetrahydro-2-(3-oxobutyl)-1*H*-pyrido[4,3-*b*]indole (11) (14·5 g., 0·052 mole) was stirred in methanol (290 ml.), and potassium borohydride (2·8 g., 0·052 mole) was added in portions with slight cooling, during ½ hr. The solution was heated under reflux for ½ hr., evaporated to a smaller volume under reduced pressure and treated with water (400 ml.) to give the *alcohol* (12·2 g., 84%) which crystallised from methanol, m.p. 169—170°. The *maleate* had m.p. 171—172° (Found: C, 57·8; H, 5·8. $C_{19}H_{23}ClN_2O_5$ requires C, 57·8; H, 5·9%).

8-*Chloro*-2-(3-*chlorobutyl*)-2,3,4,5-*tetrahydro*-1H-*pyrido*-[4,3-b]*indole*.—A solution of the carbinol (14) (4·3 g., 0·014 mole) in benzene (80 ml.) was treated with thionyl chloride (3·4 g., 0·028 mole), and heated under reflux for 5 hr. The mixture was made alkaline with dilute ammonia, and the benzene layer was separated, washed with water, dried, and evaporated. The residual *chloro-butyl compound* crystallised from ethanol–light petroleum as a pale yellow solid (3·1 g., 73·5%), m.p. 132° (Found: C, 60·3; H, 6·1; Cl, 23·6; N, 9·4. $C_{15}H_{18}Cl_2N_2$ requires C, 60·6; H, 6·1; Cl, 23·9; N, 9·4%), $\lambda_{max.}$ (EtOH) 209, 233, 291, and 301, $\lambda_{min.}$ 213, 253, and 298 mμ (log ε 4·32, 4·54, 3·82, 3·74, 4·24, 3·24, and 3·72).

2-*n*-*Butyl*-2,3,4,5-*tetrahydro*-1H-*pyrido*[4,3-b]*indole* (22).—A solution of the above chloro-butyl compound (1·5 g., 0·005 mole) liquid ammonia (150 ml.)–tetrahydrofuran (50 ml.) was treated with sodium (0·46 g., 0·02 mole); reduction was rapid. After addition of a slight excess of ammonium chloride, the mixture was evaporated to dryness, water was added, and the product was extracted with benzene. The extract was washed, dried, and evaporated, and the residue (1·4 g.) was crystallised from ethanol–light petroleum, to yield the dechlorinated *base*, m.p. 111°, $\lambda_{max.}$ (EtOH) 225, 283, and 291, $\lambda_{min.}$ 248 and 289 mμ (log ε 4·52, 3·85, 3·77, 3·31, and 3·76). The *hydrochloride* had m.p. 235° (Found: C, 68·3; H, 8·1; Cl, 13·4; N, 10·7. $C_{15}H_{20}N_2$,HCl requires C, 68·0; H, 8·0; Cl, 13·4; N, 10·6%). The base proved identical with compound (22) prepared from phenylhydrazine and *N*-n-butyl-4-piperidone (see Table 2).

8-*Chloro*-2-(2-*ethoxycarbonylethyl*)-2,3,4,5-*tetrahydro*-1H-*pyrido*[4,3-b]*indole* (15).— 8-Chloro-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (1) (6·2 g., 1 mol.) and ethyl acrylate (3·4 ml., 1·05 mol.) were heated under reflux for 6 hr. in ethanol (30 ml.), and then evaporated under reduced pressure. Crystallisation of the residue from ethanol yielded the *basic ester* (5·1 g., 56%), m.p. 120°. The *maleate* had m.p. 166—167° (Found: C, 56·4; H, 5·5. $C_{20}H_{23}ClN_2O_6$ requires C, 56·8; H, 5·5%).

8-*Chloro*-2,3,4,5-*tetrahydro*-2-[3-(3,4,5-*trimethoxybenzoyl*-

oxybutyl)]-1H-*pyrido*[4,3-b]*indole* (16).— 8-Chloro-2,3,4,5-tetrahydro-2-(3-hydroxybutyl)-1*H*-pyrido[4,3-*b*]indole (14) (5·57 g., 1 mol.), and 3,4,5-trimethoxybenzoyl chloride (9·22 g., 2 mol.) were dissolved in dry pyridine (70 ml.), and kept for 18 hr. at 20°. After evaporation under reduced pressure the residue was treated with ether and 2N-sodium hydroxide and the aqueous layer was re-extracted with ether. The dried ether solution yielded a product which crystallised from benzene to give the *ester* (2·97 g., 31%), m.p. 177—178°. The *maleate* had m.p. 183—184° (Found: C, 59·1; H, 5·65. $C_{29}H_{33}ClN_2O_9$ requires C, 59·1; H, 5·65.

8-*Chloro*-2,3,4,5-*tetrahydro*-2-[3-(*hydroxydiphenylacetoxybutyl*)]-1H-*pyrido*[4,3-b]*indole*(17).— 8-Chloro-2,3,4,5-tetrahydro-2-(3-hydroxybutyl)-1*H*-pyrido[4,3-*b*]indole (14) (5·57 g., 0·02 mole), and α-chlorodiphenylacetylchloride (5·3 g., 0·02 mole), were kept in dioxan (24 ml.) for 12 days at 20°; the solid product was filtered off, washed, and dried, to yield 8-*chloro*-2-(3-*chlorodiphenylacetoxybutyl*)-2,3,4,5-*tetrahydro*-1H-*pyrido*[4,3-b]*indole hydrochloride*, m.p. 150° (Found: N, 4·8. $C_{29}H_{28}Cl_2N_2O_2$,HCl requires N, 5·15%). The hydrochloride was suspended in water (50 ml.) and stirred vigorously at 90—95° for 20 min., after which the mixture was cooled, and treated with excess of ammonia. Ether extraction yielded a product (6·1 g.) from which the *ester hydrochloride* was prepared and crystallised from butanol, m.p. 136—138°.

Ethyl 3,3'-(3,4-*Dimethoxyphenethylimino*)*dipropionate*.— 3,4-Dimethoxyphenethylamine (101 g., 0·56 mole), ethyl acrylate (500 ml., large excess), and cuprous chloride (1·0 g.) were heated under reflux for 20 hr. The excess of acrylate was evaporated, and the residue was treated with ether and excess of 2N-sulphuric acid. After re-extraction of the ether with fresh acid, the acid layers were made alkaline with ammonia, and extracted with ether. The dried ether solution, on evaporation, yielded the crude basic diester (100%). The *hydrochloride*, m.p. 103—104° crystallised from isopropyl alcohol–ether as plates (Found: C, 57·5; H, 7·9; Cl, 9·0; N, 3·4. $C_{20}H_{31}NO_6$,HCl requires C, 57·5; H, 7·7; Cl, 8·5; N, 3·35%). Under less vigorous conditions (short reflux, no cuprous chloride), appreciable amounts of ethyl 3-(3,4-dimethoxyphenethyl)aminopropionate were obtained. The *hydrochloride* forms rods, m.p. 150—151° (Found: C, 56·9; H, 7·6; Cl, 11·5; N, 4·5. $C_{15}H_{23}NO_4$,HCl requires C, 56·7; H, 7·6; Cl, 11·2; N, 4·4%).

1-(3,4-*Dimethoxyphenethyl*)-3-*ethoxycarbonyl*-4-*piperidone*.—Ethyl 3,3'-(3,4-dimethoxyphenethylimino)dipropionate (68·6 g., 0·18 mole) was added to powdered sodium (13·6 g., 0·59 mole) in toluene (1l.); ethanol (2 ml.) was added, and the mixture was stirred and heated cautiously, until a moderately vigorous reaction occurred. When this had subsided, a further quantity of the diester (137·2 g., 0·36 mole) was added at such a rate that gentle reflux was maintained, and, finally, stirring and refluxing was maintained for 1 hr. The mixture was cooled and extracted with 2N-hydrochloric acid, and the acid layer was made alkaline with ammonia, and extracted with ether. The dried ether yielded the ethoxycarbonyl-piperidone, which was converted into a *hydrochloride* (139 g., 69%), m.p. 177—178° (Found: C, 58·0; H, 7·4; Cl, 9·2; N, 3·7. $C_{18}H_{25}NO_5$,HCl requires C, 58·1; H, 7·05; Cl, 9·5; N, 3·8%).

1-(3,4-*Dimethoxyphenethyl*)-4-*piperidone*.— 1-(3,4-Dimethoxyphenethyl)-3-ethoxycarbonyl-4-piperidone hydrochloride (50·2 g., 0·131 mole) was boiled with 2N-hydrochloric acid (500 ml.) for 9 hr., after which the solution had a negative reaction to ferric chloride. The solution was cooled, made alkaline with solid potassium carbonate, and extracted several times with ether. The dried ether yielded an oil (32 g.) which crystallised from ethanol to yield the *piperidone* (27·6 g., 79·8%), m.p. 79° (Found: C, 68·6; H, 8·2. $C_{15}H_{21}NO_3$ requires C, 68·4; H, 8·0%).

Hydrogenation of 2-*Benzyl*-8-*chloro*-2,3,4,5-*tetrahydro*-1H-*pyrido*[4,3-b]*indole* (9).—The pyridoindole (0·62 g., 0·0021 mole) was hydrogenated in ethanol (50 ml.) in the presence of 5% palladium–strontium carbonate (0·4 g.) until 2 molar proportions of hydrogen had been absorbed. The filtrate yielded 2,3,4,5-*tetrahydro*-1H-*pyrido*[4,3-b]*indole hydrochloride*, m.p. 255° (Found: Cl, 16·8; N, 13·7. $C_{11}H_{12}N_2$,HCl requires Cl, 17·0; N, 13·4%). The free base (19) crystallised from ethanol–light petroleum, m.p. 215—216° (lit.,[6] 215·5°).

Hydrogenation of 8-*Chloro*-2,3,4,5-*tetrahydro*-2-*methyl*-1H-*pyrido*[4,3-b]*indole hydrochloride* (2).—The hydrochloride (1·28 g., 0·005 mole) in water (128 ml.) was hydrogenated in the presence of pre-hydrogenated palladium oxide (0·1 g.); 1 mol. hydrogen was absorbed in 7 hr. The filtrate was made alkaline, and the resulting product was crystallised from benzene to yield 2,3,4,5-tetrahydro-2-methyl-1*H*-pyrido[4,3-*b*]indole (20), m.p. 171—172° (lit.,[7b] 171—172°).

4-*Chloro*-2-*methylphenylhydrazine*.—This compound was obtained in 70% yield by the general method of Hunsberger *et al.*[16] The *base* crystallised from ethanol, m.p. 113—114° (Found: C, 53·3; H, 5·85; Cl, 22·8. $C_7H_9ClN_2$ requires C, 53·7; H, 5·8; Cl, 22·6%). The hydrochloride had m.p. 219—220° (Found: C, 43·7; H, 5·2; N, 14·7. Calc. for $C_7H_9ClN_2$,HCl: C, 43·55; H, 5·2; N, 14·5%) [lit.,[17] m.p. 201—202° (decomp.)].

The following compounds were also made by Hunsberger's method. 2,3-Dichlorophenylhydrazine, m.p. 114—115° (lit.,[18] 113·4—115·4°). The hydrochloride had m.p. 253° (Found: Cl, 49·6; N, 13·2. Calc. for $C_6H_6Cl_2N_2$,HCl: Cl, 49·8; N, 13·1%) (lit.,[16] m.p. 241—242°).

m-Propoxyphenylhydrazine, b.p. 118—120°/0·1 mm. (yield 38%), *hydrochloride*, m.p. 152—153° from ethanol–light petroleum (Found: C, 53·3; H, 7·4; Cl, 17·4. $C_9H_{14}N_2O$,HCl requires C, 53·3; H, 7·5; N, 17·5%).

m-Butoxyphenylhydrazine, b.p. 138—142°/0·2 mm. (slight decomp.) (yield 59·5%), *hydrochloride*, m.p. 137°, from ethanol–light petroleum (Found: C, 55·3; H, 7·9; Cl, 16·1. $C_{10}H_{16}N_2O$,HCl requires C, 55·4; H, 7·9; Cl, 16·4%).

2-*Chloro*-3-*methoxyphenylhydrazine*, m.p. 77—78° from light petroleum (yield 55·1%) (Found: Cl, 20·7; N, 16·3. $C_7H_9ClN_2O$ requires Cl, 20·5; N, 16·2%).

2-Chloro-5-methoxyphenylhydrazine, m.p. 70—71° from ethanol (yield 36%) (Found: Cl, 20·7; N, 16·1. Calc. for $C_7H_9ClN_2O$: Cl, 20·5; N, 16·2%) (lit.,[19] m.p. 70—72·5°).

6,7-*Dichloro*-2,3,4,5-*tetrahydro*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (27).—2,3-Dichlorophenylhydrazine (13·3 g., 0·075 mole), and 1-methyl-4-piperidone (8·5 g., 0·075 mole) in ethanol (60 ml.) were heated under reflux for 1 hr. After

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[17] M. W. Bullock and J. J. Hand, *J. Amer. Chem. Soc.*, 1956, **78**, 5854.
[18] U.S.P. 2,879,270/1959.
[19] B. Clifford, P. Nixon, C. Salt, and M. L. Tomlinson, *J. Chem. Soc.*, 1961, 3518.

evaporation under reduced pressure treatment with light petroleum yielded 1-*methyl*-4-*piperidone*-2,3-*dichlorophenylhydrazone* (14·8 g., 73%), m.p. 57°. On further crystallisation the m.p. rose to 60—62° (Found: C, 52·9; H, 5·5. $C_{12}H_{15}Cl_2N_3$ requires C, 52·9; H, 5·55%).

Polyphosphoric acid (40 g.) was heated to 100°, and the above hydrazone (10·2 g., 0·0376 mole) was added in small portions with stirring. An exothermic reaction occured, but the temperature was kept at 100—110° by cooling. Finally, the mixture was cautiously warmed to 150°, and then allowed to cool. The dark gummy mass was extracted with hot water (60 ml.), shaken with charcoal, and filtered. The extract was treated with excess of 2N-sodium hydroxide and ether, filtered from insoluble tar, and re-extracted with fresh ether. Evaporation of the dried ether yielded solid (3·5 g.) which was crystallised from ethanol to yield the *tetrahydropyridindole* (2·3 g., 24%), m.p. 165°. The *methanesulphonate* had m.p. 246—248° (Found: C, 44·7; H, 4·65. $C_{13}H_{16}Cl_2N_2O_3S$ requires C, 44·4; H, 4·6%).

7- (*or* 9)-*Trifluoromethyl*-2,3,4,5-*tetrahydro*-1H-*pyrido*-[4,3-b]*indole* (29).—4-Piperidone hydrochloride (13·1 g., 0·097 mole) and *m*-trifluoromethylphenylhydrazine (17·1 g., 0·097 mole) in methanol (30 ml.) containing a drop of 2N-hydrochloric acid were heated under reflux for ¾ hr., and evaporated under reduced pressure. The residue was heated for 1 hr. at 85° with a mixture of concentrated sulphuric acid (21 ml.), and acetic acid (126 ml.) after which it was cooled, diluted with water, and made alkaline. The crude product (11 g.) was crystallised from methanol, after charcoal treatment, to yield the *tetrahydropyridoindole* (2·3 g., 10%), m.p. 233°. The *maleate* crystallised from water, m.p. 179—180° (Found: C, 53·7; H, 4·4; N, 7·5. $C_{16}H_{15}F_3N_2O_4$ requires C, 53·9; H, 4·2; N, 7·9%).

7- (*or* 9)-*Trifluoromethyl*-2,3,4,5-*tetrahydro*-2-*methyl*-1H-*pyrido*[4,3-b]*indole* (30).—1-Methyl-4-piperidone (5·2 g., 0·046 mole), and *m*-trifluoromethylphenylhydrazine hydrochloride (9·8 g., 0·046 mole) in methanol (20 ml.) containing a drop of 2N-hydrochloric acid were treated as described above. The crude cyclisation product (8·3 g., m.p. *ca.* 200°) was crystallised from ethyl acetate or dioxan and yielded the *tetrahydropyridoindole* (5·5 g., 47%), m.p. 229—232°. The *hydrochloride* crystallised from 0·5N-hydrochloric acid, m.p. 254—255° (Found: C, 53·2; H, 5·1; Cl, 12·2; H_2O (by Karl Fischer), 1·6. $C_{13}H_{13}F_3N_2$,HCl,0·25H_2O requires C, 52·9; H, 4·95; Cl, 12·0; H_2O, 1·5%). Aksanova *et al.*[11] have given m.p. 232—233° for a base probably identical with that described above. Their hydrochloride had m.p. 242—244°.

8-*Trifluoromethyl*-2,3,4,5-*tetrahydro*-2-*methyl*-1H-*pyrido*-[4,3-b]*indole* (31).—*N*-Methyl-4-piperidone (2·26 g., 0·02 mole), and *p*-trifluoromethylphenylhydrazine (3·52 g., 0·02 mole) were heated under reflux in ethanol (16 ml.) for 15 min. and then the mixture was evaporated under reduced pressure. Treatment of the residue with light petroleum gave a hydrazone (4·8 g., 88%), m.p. 72—76°. The hydrazone (6·1 g., 0·0235 mole) was cyclised as described for the 7-trifluoromethyl isomer and yielded a product (3·35 g., 59%), m.p. 180—182°. which was converted into the *tetrahydropyridoindole hydrochloride*. The latter crystallised from 4N-hydrochloric acid, m.p. 273—275° (Found: Cl, 12·1. $C_{13}H_{13}F_3N_2$,HCl requires Cl, 12·2%). The free *base* obtained from the hydrochloride crystallised from benzene, m.p. 180—182°.

2,3,4,5-*Tetrahydro*-7-*methoxy*-2-*methyl*-1H-*pyrido*[4,3-b]*indole* (33).—Sodium (0·4 g., 0·0176 g.-atom) was added to a stirred suspension of 6-chloro-2,3,4,5-tetrahydro-7-methoxy-2-methyl-1*H*-pyrido[4,3-*b*]indole (37) (2 g., 0·008 mole) in liquid ammonia (150 ml.). After a permanent blue colour had been obtained, the mixture was decomposed with ammonium chloride, the ammonia was evaporated, and the solid product was washed with water, dried, and crystallised from ethanol (50 ml.) to give the chlorine-free *base* as a white solid (1·1 g., 64·5%), m.p. 195—196°. When *m*-methoxyphenylhydrazine (56 g., 0·4 mole), and 1-methyl-4-piperidone (46 g., 0·4 mole) were allowed to react under the general conditions already described, the same product, m.p. 195—196°, was obtained (59·5 g., 68%). The bases made by the two methods were identical (m.p., mixed m.p., and i.r. spectra). The *hydrochloride*, prepared from base, obtained by either of the above two methods had m.p. and mixed m.p., 234—235° (Found: Cl, 13·9. $C_{13}H_{16}N_2O$,HCl requires Cl, 14·0%).

7-*Ethoxy*-2,3,4,5-*tetrahydro*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (38).— 2,3,4,5-Tetrahydro-7-hydroxy-2-methyl-1*H*-pyrido[4,3-*b*]indole hydrobromide (44, see below) (5·6 g., 0·02 mole) was stirred in ethanol (100 ml.), and treated with 2N-sodium hydroxide solution (20 ml., 0·04 mole). Ethyl sulphate (3·1 g., 0·02 mole) was added, and the mixture was stirred for 40 min. at 50°, after which most of the solvent was evaporated under reduced pressure. The gummy residue was triturated with N-sodium hydroxide and then with water, and finally filtered to give the crude product (2·0 g.). Crystallisation from ethyl acetate–chloroform gave the *ether* (0·71 g.), m.p. 195°. A second crop (0·2 g., total 20%) was obtained after purification on alumina. After recrystallisation from methanol, the m.p. was 199—200°. The *hydrochloride* crystallised from N-hydrochloric acid, m.p. 235° (Found: Cl, 13·2; N, 10·5. $C_{14}H_{18}N_2O$,HCl requires Cl, 13·3; N, 10·5%).

8-*Benzyloxy*-2,3,4,5-*tetrahydro*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (41).—*p*-Benzyloxyphenylhydrazine (1·9 g., 0·0088 mole), and 1-methyl-4-piperidone (1·0 g., 0·0088 mole) were dissolved in a mixture of acetic acid (16 ml.), and water (8 ml.) at 20°. After 1½ hr. the mixture was warmed to 50° for 1 hr., and then evaporated under reduced pressure. The residue was boiled with 2N-ethanolic hydrogen chloride (25 ml.) for 1 hr., filtered, and allowed to cool. The crystalline product (1·7 g., 58%) was recrystallised from water, after charcoal treatment, to yield the *hydrochloride*, m.p. 234—235°.

2,3,4,5-*Tetrahydro*-9-*methoxy*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (42).— 6-Chloro-2,3,4,5-tetrahydro-9-methoxy-2-methyl-1*H*-pyrido[4,3-*b*]indole (43) (2 g., 0·008 mole) in ethanol (100 ml.) was hydrogenated for 20 hr. at atmospheric pressure in the presence of palladium–charcoal catalyst (1 g., 10% Pd.). The catalyst was filtered off, and the filtrate was evaporated to a small volume, when the *hydrochloride* crystallised as needles (1·53 g., 75·4%), m.p. 263° (Found: C, 61·8; H, 6·7; Cl, 14·4; N, 10·8. $C_{13}H_{16}N_2O$,HCl requires C, 61·8; H, 6·8; Cl, 14·0; N, 11·1%). The *base* crystallised as prisms from methanol, m.p. 184—185°.

2,3,4,5-*Tetrahydro*-7-*hydroxy*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (44).—A solution of the 7-methoxy-derivative described above (33) (49·5 g., 0·228 mole) was boiled in constant-boiling hydrobromic acid (225 ml.) for 20 min., and cooled. After several hours the solid obtained was filtered off, washed with ice-water, and dried (27 g.), m.p. *ca.* 220°. Crystallisation from methanol yielded the *hydrobromide* (20 g., 31%), m.p. 234—235°. The *hydrochloride* crystallised from

2N-hydrochloric acid, m.p. *ca.* 250° (Found: C, 60·5; H, 6·3. $C_{12}H_{14}N_2O$,HCl requires C, 60·4; H, 6·3%). The above hydrobromide, m.p. 234—235° was also obtained when 7-propoxy- and 7-n-butoxy-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole, (prepared by the general method) were dealkylated in the manner described.

2,3,4,5-*Tetrahydro*-8-*hydroxy*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (45).—The benzyl ether hydrochloride (41) (3·65 g., 0·011 mole) was suspended in water (100 ml.) at 70° and hydrogenated in the presence of palladium–charcoal (0·36 g., 20% Pd) at 1 atmosphere pressure. Absorption was complete in 1 hr.; the solution was filtered, evaporated under reduced pressure and the residual solid was crystallised from water (12 ml.) to give the *hydrochloride* (1·8 g., 69%), m.p. *ca.* 285° (decomp.).

2,3,4,5-*Tetrahydro*-9-*hydroxy*-2-*methyl*-1H-*pyrido*[4,3-b]-*indole* (46).—A solution of the 9-methoxy-compound (42) (1·7 g., 0·008 mole) in constant-boiling hydrobromic acid (8·6 ml.) was heated under reflux for 20 min. It was then cooled, evaporated to a small volume under reduced pressure, diluted with ethyl alcohol (70 ml.), and allowed to crystallise. The crude product (0·48 g., 21·2%) crystallised from ethyl alcohol to give the *hydrobromide*, m.p. *ca.* 285°.

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Derivatives of Indole in an Attempted Cyclisation of *o*-Nitrophenylsuccinic Acid

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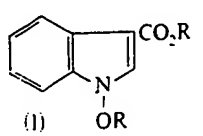
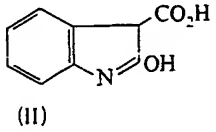
Treatment of *o*-nitrophenylsuccinic anhydride with fluorosulphonic acid at steam-bath temperature gave 1-hydroxyindole-3-carboxylic acid and oxindolic acid.

UNDER Friedel–Crafts conditions *o*-nitrophenylpropionic acid can be cyclised to give 4-nitroindanone.[1] In this singular cyclisation the nitro-group may be sterically prevented from exerting its full deactivating effect by the adjacent side chain. We attempted to cyclise *o*-nitrophenylsuccinic acid and its anhydride, compounds in which this steric effect would be enhanced. No experiments on the acid chloride could be made as all attempts to prepare this led to the anhydride only. *o*-Nitrophenylsuccinic acid was unchanged by the action of anhydrous hydrogen fluoride and gave tarry products when heated with polyphosphoric acid. The anhydride could not be cyclised under Friedel–Crafts conditions using ethylene dichloride or nitrobenzene as solvent, and when heated with polyphosphoric acid gave unchanged anhydride and tarry material only. When *o*-nitrophenylsuccinic anhydride was heated with fluorosulphonic acid no ketone was formed but two heterocyclic acids both having an equivalent weight of 180 could be isolated. The structures (I; R = H) and (II)



(I)



(II)

have been assigned to these compounds; they provide a further example of the reactions of nitro-groups with neighbouring groups which have been reviewed by Loudon and Tennant.[2]

Compound (I; R = H) could be acetylated and the i.r. spectrum of the crude product showed a peak at 1800 cm.$^{-1}$ found in *N*-acetoxy-compounds.[3] It was methylated by diazomethane to give a methoxy-ester (I; R = Me) the n.m.r. spectrum of which showed a multiplet for four aromatic protons, centre τ 2·29, a singlet for one proton at τ 3·95 (ethylenic H), two singlets each for three protons at τ 5·91 (=N·OMe) [4] and τ 6·03 (CO_2Me). The product from the action of toluene-*p*-sulphonyl chloride and sodium hydroxide solution was spectroscopically and chromatographically identical with a sample of indigotin, a remarkable transformation which gave supporting evidence that (I) was a derivative of indole. Compound (I; R = H) differed from the known *N*-hydroxyindole-2-carboxylic acid [5] and the 3-isomer remained as the only structure consistent with the evidence. A carbonyl peak at 1654 cm.$^{-1}$ in its i.r. spectrum confirmed that (I; R = H) had a carboxyl group at position 3; this peak occurs in indole-2-carboxylic acids at higher frequencies.[6] Attempts using various reagents to reduce (I; R = H or R = Me) to indole-3-carboxylic acid gave a compound to which the structure *NN'*-bi-indolyl-3,3'-dicarboxylic acid has been assigned. The i.r. spectrum of this compound showed no peak due to NH. The n.m.r. spectrum in trifluoroacetic acid showed no peak due to NH, a multiplet, centre τ 2·04 for four aromatic protons and a singlet

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